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(71) **ABBOTT LABORATORIES,**
D377 AP6D
100 Abbott Park Road, ABBOTT ROAD, XX (US).

(72) **GILBERT, ADRIENNE L. (US).**
DEATON, ROGER L. (US).
GIARDINA, WILLIAM J. (US).
COLLINS, STEPHEN D. (US).

(74) **TORYS LLP**

(54) UTILISATION DE TIAGABINE POUR LE TRAITEMENT DE NEUROPATHIE ET DE MIGRAINE LIEES AU DIABETE

(54) THE USE OF TIAGABINE FOR TREATMENT OF DIABETIC NEUROPATHY AND MIGRAINE

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(71) Demandeur/Applicant:
ABBOTT LABORATORIES, US

(72) Inventeurs/Inventors:
COLLINS, STEPHEN D., US;
DEATON, ROGER L., US;
GIARDINA, WILLIAM J., US;
GILBERT, ADRIENNE L., US

(74) Agent: TORYS LLP

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(71) Applicant: **ABBOTT LABORATORIES** [US/US]; D377 AP6D, 100 Abbott Park Road, Abbott Road, IL 60064-6050 (US).

(72) Inventors: **COLLINS, Stephen, D.**; 1543 West Durham Drive, Inverness, IL 60067 (US). **DEATON, Roger, L.**; 16705 West Cherrywood Lane, Wadsworth, IL 60083 (US). **GIARDINA, William, J.**; 707 Eton Court, Libertyville, IL 60048 (US). **GILBERT, Adrienne, L.**; 388 East Pine Lake Circle, Vernon Hills, IL 60061 (US).

(74) Agents: **WARD, Michael, J.** et al.; Abbott Laboratories, 100 Abbott Park Road, D377 AP6D/2, Abbott Park, IL 60064-6050 (US).

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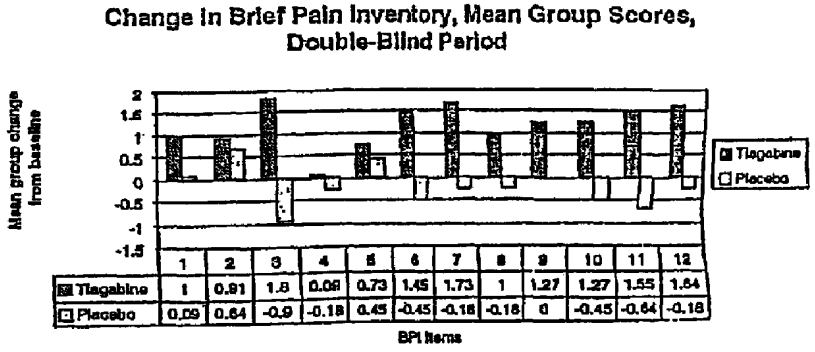

	1	2	3	4	5	6	7	8	9	10	11	12
Tiagabine	1	0.91	1.8	0.09	0.73	1.45	1.73	1	1.27	1.27	1.55	1.64
Placebo	0.09	0.64	-0.9	-0.18	0.45	-0.45	-0.18	-0.18	0	-0.45	-0.64	-0.18

(57) Abstract: (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid and salts thereof are effective GABA uptake inhibitory compounds and exert pharmacological effects on pain associated with diabetic neuropathy and migraine.

BPI Items

1. Worst pain intensity in last 24 hours.
2. Average pain intensity since last visit.
3. Percentage of relief in last 24 hours. (Divided by 10)
4. Pain intensity right now.
5. Least pain intensity in last 24 hours.
6. Interference with general activity in last 24 hours.
7. Interference with mood in last 24 hours.
8. Interference with walking ability in last 24 hours.
9. Interference with normal work in last 24 hours.
10. Interference with relations with other people in last 24 hours.
11. Interference with sleep in last 24 hours.
12. Interference with enjoyment of life in last 24 hours.

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THE USE OF TIAGABINE FOR TREATMENT OF DIABETIC NEUROPATHY AND MIGRAINE

BACKGROUND OF THE INVENTION

In the last two decades, intensive pharmacological research concerning gamma-aminobutyric acid (GABA), a neurotransmitter in the central nervous system, has taken place.

Compounds which increase GABA activity are useful in the treatment of anxiety, epilepsy and muscular and movement disorders. Furthermore, these compounds can be used as sedatives.

In U.S. Pat. Nos. 4,383,999 and 4,514,414 (Smithkline Beckman Corporation) some derivatives of N-(4-phenylbuten-3-yl)azaheterocyclic carboxylic acids which have, furthermore, inter alia, phenyl, 4-fluorophenyl, cyclohexyl or thienyl in the 4-position, are described. It is stated therein that the compounds are useful as inhibitors of GABA uptake.

According to *J. Pharm. Exp. Therap.*, 228 (1984), 109 et seq., N-(4,4-diphenyl-3-butenyl)nipecotic acid (designated SK&F 89976A). N-(4,4-diphenyl-3-butenyl)guvacine (designated SK&F 100330A), N-(4,4-diphenyl-3-butenyl)-*B*-homoproline (designated SK&F 100561) and N-(4-phenyl-4-(2-thienyl)-3-butenyl)nipecotic acid (designated SK&F 100604J) are active inhibitors of GABA uptake.

It is further well recognized in the art that *B*-homo-proline, nipecotic acid and guvacine are biological equivalents, at least as far as their GABA-like effects regards. See for example Progress in Medicinal Chemistry 21, 67-120 (1985); ed. Ellis West; Elsevier Science Publishers; Molecular and Cellular Biochemistry 31, 105-121 (1980), and *J. Pharm. Exp. Therap.*, 228 (1984), 109 et seq.

US 5,010,090 teaches the use of N-(Butenyl Substituted) Aza-Hetreocyclic Carboxylic Acids as exhibiting GABA uptake inhibitory properties. In particular, N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid and salts thereof are effective GABA

uptake inhibitory compounds. These compounds have been found to be effective in the treatment of chronic pain.

A study evaluated tiagabine HCl in animal models of neuropathic and nociceptive pain. An Evaluation of the GABA Uptake Blocker Tiagabine in Animal Models of Neuropathic and Nociceptive Pain, A. Giardina et al. The study did not evaluate the effects of tiagabine HCl in treating humans or pain associated with diabetic polyneuropathy and migraine.

FIGURES

Figure 1 depicts a list of the BPI items and the Change in Brief Pain Inventory in the Double-blind study comparing tiagabine XR to placebo. The ratings for the BPI items may range from 0-10 (except 0%-100% for item 3). The results indicated that tiagabine XR improved scores in all 12 parameters and the positive effect of tiagabine XR was statistically significant in items 3 and 11. Mean changes in the two scores are displayed as improvements from baseline such as that a positive change reflects improvement and a negative change reflects worsening.

Figure 2 is a listing of the BPI items asked during the double-blind study.

DETAILED DESCRIPTION OF THIS INVENTION

It has been found that (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid and salts thereof are effective GABA uptake inhibitory compounds and exert pharmacological effects on pain associated with diabetic neuropathy and migraine. (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic hydrochloride (Tiagabine HCl, (Gabitril®) is sold commercially as an anti-epileptic. It is to be understood that isomers, including enantiomers, are included within the scope of this invention. US 5,010,090 teaches the synthesis and use of N-(Butenyl Substituted) Aza-Hetreocyclic Carboxylic Acids as exhibiting GABA uptake inhibitory properties. US 5,010,090 is hereby entirely incorporated by reference.

An extended release formulation of (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride (Tiagabine XR) (Formula G, 7507-9; Abbott Laboratories, IL.) was used for the treatment of pain associated with diabetic

polyneuropathy. Tiagabine XR formulations useful include tiagabine and high molecular weight polyethylene oxide formulations that are exemplified in WO 99/37302, which published July 29, 1999. WO 99/37302 is hereby fully incorporated by reference.

A single-center pilot study with an initial Open-Label Phase, followed by a randomized, double-blind, placebo-controlled, two-period, crossover phase, for subjects who demonstrated a reduction in their pain during the Open-Label Phase. The Open-Label Phase consisted of a Screening Period of up to 14 days and an up to 6-week Dose-Evaluation Period. The Double-Blind Phase consisted of two 1 to 5 week(s) treatment periods, each preceded by a 1-week Washout Period. The actual duration of the study was to have varied from subject to subject and was to range from 9 to 19 weeks for those who qualified for the Double-Blind Phase, depending on the maximum tolerated dose (MTD) of tiagabine XR established during the Open-Label Phase.

The Open-Label Phase study evaluated 35 patients with painful diabetic polyneuropathy. Patients were initially titrated to their maximum tolerated dose of an extended release formulation of tiagabine hydrochloride (tiagabine XR) (Abbott Laboratories, Abbott Park, IL.) and were assessed by the Brief Pain Inventory (BPI). the BPI is hereby incorporated by reference. Patients successfully tolerating a daily dose of at least 12 mg (max: 60 mg) who demonstrated pain relief of at least three units on the worst/average pain items of the BPI were randomized, washed out, and re-titrated to their previously tolerated dose in a two-period, double-blind, placebo-controlled crossover phase.

Males or non-pregnant, non-lactating females at least 18 years of age, diagnosed with stable chronic pain for at least 3 months, who met diagnostic criteria for generalized, symmetrical, painful diabetic polyneuropathy and had a pain rating of 3 units or higher on the worst pain item of the BPI at Visit 1 were eligible for study participation. Figure 2 provides a listing of the BPI items. Additionally, subjects who were on a fixed-schedule analgesic regimen must have been on a stable dose for 14 days prior to Visit 1. Subjects with a current seizure disorder or with a significant neurologic or psychiatric illness or impairment were not eligible for study participation.

Subjects entering the Dose-Evaluation started tiagabine XR dosing at 12 mg/day for 1 week. Each week thereafter the dose of tiagabine XR was increased by 12 mg/day up to a maximum of 60 mg/day. The Dose-Evaluation Period ended after 1 week of stable dosing at the MTD. Subjects who demonstrated a reduction from Visit 1 of at least 2 units in either the worst pain or average pain items of the BPI and met all other randomization criteria entered the Double-Blind Phase.

Subjects who met the criteria for entry into the Double-Blind Phase were randomly assigned in equal numbers to one of two treatment sequences:

Sequence Group 1: Placebo (Treatment Period I): tiagabine XR (Treatment Period II)

Sequence Group 2: Tiagabine XR (Treatment Period 1): placebo (Treatment Period II)

The Double-Blind Phase consisted of two equal-length treatment periods; each preceded by a 1-week Washout Period. Throughout the study, the BPI was used to assess the subject's pain

Seventeen subjects completed the open-label dose evaluation period. Five did not identify sufficient pain reduction (3 units in either the worst pain or average pain items of the BPI) to qualify for randomization. One declined for personal reasons. All 11 randomized subjects completed the Double-Blind Phase of the study.

Statistically significant differences favoring tiagabine XR were observed for: 1) change in percent pain relief in the last 24 hours and 2) extent that pain interfered with sleep during the last 24 hours (see Figure 1). Improvement trends favoring tiagabine XR were observed in all planned BPI variables. All randomized subjects completed the study. In this study, tiagabine XR was safe and demonstrated a consistent trend in pain improvement in patients with diabetic polyneuropathy.

The statistically significant differences ($P \leq 0.05$) during the double-blind phase favoring tiagabine XR were observed for the changes in percent of pain relief that the treatment had provided in the last 24 hours and the extent that pain had interfered with sleep in the last 24 hours. Improvement favoring tiagabine XR, though not statistically

significantly different from placebo, were observed in all the other pre-planned BPI variables. The most notable treatment differences occurred in the BPI items pertaining to the extent that pain in the last 24 hours had interfered with relations to people, general activity, enjoyment of life, and mood. Tiagabine XR demonstrated positive effects in both the Dose-Evaluation Period (open-label treatment) and the Double-Blind Phase.

WE CLAIM:

1. A method of treating pain associated with diabetic polyneuropathy by administering a pharaceutically effective amount of the compound (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride.

2. A method of claim 1 wherein said (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride is in an extended release formulation.

3. A method of treating migraine by administering a pharaceutically effective amount of (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride.

4. A method of claim 3 wherein said (R)-N-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid hydrochloride is in an extended release formulation.

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13ter.1(c) and Rule 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing *(day/month/year)*
6744.PC.01		08/05/2002
International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US 01/51407	19/10/2001	20/10/2000
International Patent Classification (IPC) or both national classification and IPC		
Applicant		
ABBOTT LABORATORIES		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below

1. ☐ The subject matter of the international application relates to:
   - a. ☐ scientific theories.
   - b. ☐ mathematical theories
   - c. ☐ plant varieties.
   - d. ☐ animal varieties.
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. ☐ schemes, rules or methods of doing business.
   - g. ☐ schemes, rules or methods of performing purely mental acts.
   - h. ☐ schemes, rules or methods of playing games.
   - i. ☐ methods for treatment of the human body by surgery or therapy.
   - j. ☐ methods for treatment of the animal body by surgery or therapy.
   - k. ☐ diagnostic methods practised on the human or animal body.
   - l. ☐ mere presentations of information.
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art.

2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
   ☒ the description ☒ the claims ☐ the drawings

3. ☐ The failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions prevents a meaningful search from being carried out:
   - ☐ the written form has not been furnished or does not comply with the standard.
   - ☐ the computer readable form has not been furnished or does not comply with the standard.

4. Further comments:

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Véronique Baillou

Form PCT/ISA/203 (July 1998)

International Application No. PCT/US 01/51407

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

A meaningful search is not possible on the basis of all claims because all claims are directed to - Method for treatment of the human or animal body by therapy - Rule 39.1(iv) PCT

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.